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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,396	12/27/2001	David Botstein	GNE.2930R1C4	1010

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EXAMINER

FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 09/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/033,396

Applicant(s)

BOTSTEIN ET AL.

Examiner

Jeffrey Fredman

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 19 July 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 22-27 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 22-27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 4/29/03 + 4/21/03
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 22-27 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The current claims are drawn to a genus of antibodies which bind to a protein termed Pro-539 (SEQ ID NO: 7) or portions thereof, in the specification, where the protein has the amino acid sequence of SEQ ID NO: 7.

Credible Utility

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the antibody or of the Pro-539 protein to which it binds. The cited utilities in the specification include overexpression in cancer. These utilities are credible.

Upon identification of credible utilities, the next issue is whether there are any well established utilities for the PRO 539 polypeptide or antibody. A review of the specification and of the prior art finds no well established utilities for unknown proteins and antibodies whose activity, whose enzymatic or other biochemical function and whose cellular roles are entirely unknown and undisclosed in the specification.

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The next inquiry is whether there are substantial or specific utilities for the antibody to PRO 539 protein which are identified in either the specification or in the prior art.

Substantial utility

Here, the evidence in the specification provided is that the nucleic acid which encodes the PRO 539 protein is overexpressed in cancer cells. The level of overexpression of PRO 539 was minimal, not even a two fold overexpression in any cell type. Further, no statistical data was presented to show that the overexpression was significant in any way, with no P-value or other statistical measure to demonstrate that the overexpression was a real effect and not simply produced by chance.

This data further lacks any of the hallmarks of utility because the overexpression of the nucleic acid is not relevant to the utility of the protein and antibody. There is no evidence that the protein itself is overexpressed. Meric et al (Molecular Cancer Therapeutics (2002) 1:971-979) in a discussion of regulation of gene activity in cancer notes that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation and protein stability (page 971, column 1)." So Meric teaches that there is not necessarily a correlation between mRNA levels and protein levels in cancer cells, since the regulation may occur at levels other than that of the mRNA, such as in the level of translation of the mRNA or in the stability of the protein.

The absence of any necessary correlation between increased mRNA levels and increased protein levels is made explicit by Gokman-Polar (Cancer Research (2001)

61:1375-1381) who teaches "Quantitative reverse transcription-PCR analysis revealed that PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isozyme expression is likely regulated at the posttranscriptional/translational level (see abstract)." Gokman-Polar show in figures 6 and 7 that there is no increase in mRNA expression for any of the isozymes, while the protein is significantly overexpressed as shown by figures 4 and 5. This demonstrates that there is no relationship between mRNA levels and protein levels.

A further evidentiary showing is provided by Pennica et al (Proc. Natl. Acad. Sci. USA (1998) 95:14717-14722) who shows that WISP-2 DNA was amplified in cancer cells but was actually demonstrated REDUCED RNA expression (see abstract). This provides additional evidence that there is no relationship between gene amplification and mRNA levels, since mRNA levels have no necessary correlation with gene amplification.

So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by Applicant showing overexpression of one component does not provide utility for the protein itself.

Further, given the breadth of these claims which encompass any antibody to the Pro-539 polypeptide, there is an abundance of evidence that very similar proteins can perform very different functions. For example, Rost et al (J. Mol. Biol. (2002) 318(2):595-608) notes regarding assignment of enzymatic activity based upon

homology comparisons that “The results illustrated how difficult it is to assess the conservation of protein function and to guarantee error-free genome annotations, in general: sets with millions of pair comparisons might not suffice to arrive at statistically significant conclusions (abstract).” Thus, even high levels of homology do not necessarily correlate with actual protein function. In the current case, where the function of PRO-539 (SEQ ID NO: 7) is not known, the expectation is even lower that there is any utility that can be derived based upon the sequence.

This situation is extremely similar to example 12 of the Utility Guidelines, where a protein which was known to be a receptor, but where the ligand was unknown, was found to lack utility. In the current case, the putative PRO-539 protein, lacks any substantial utility whatsoever, and solely relies upon an small level of mRNA overexpression in cancer cells. However, there is no necessary relationship between the protein levels or utilities and such an overexpression of the nucleic acid. So this case is also similar to the receptor in Example 12, since it lacks a substantial utility because there is no “real world” context of use. Further research would be required to identify and reasonably confirm a “real world” context of use for PRO-539 antibodies and proteins. As noted in the utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials).

Specific Utility

In the current case, even if the substantial utility argument above were found unpersuasive, there is no specific utility given for the antibody to the PRO-539 protein of

SEQ ID NO: 7. The antibody to the protein, as distinguished from the nucleic acid, has not been associated with any disease, any condition, or any other specific feature.

There is no association of the antibody or protein with cancer or with any other disease.

As the utility guideline training materials note on page 5-6, "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed". Here, the overexpression of the nucleic acid gives no specific utility because it is entirely unrelated to uses of the protein or antibody. A protein or antibody cannot be used to detect changes in its cognate nucleic acid, as shown by the Gokman-Polar and Meric papers, where protein levels are not correlative with nucleic acid levels. Therefore, there is no specific utility for this protein until a specific ligand is identified.

Finally, with regard to the utility analysis, the current situation directly tracks Examples 4 and 12 of the utility guidelines, where a protein of entirely unknown function and a receptor with an unknown ligand was characterized as lacking utility.

Claim Rejections - 35 USC § 112 – Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 22-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention

The claims are drawn to an antibody to the PRO-539 protein of SEQ ID NO: 7. The invention is in a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims broadly encompass not only a particular PRO-539 antibody but also include any antibody which binds the polypeptide of SEQ ID NO: 7.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the activity of polypeptides and nucleic acids. It would require significant study to identify the actual function of the PRO-539 protein and nucleic acid, and identifying a use for this protein and resultant antibody would be an inventive, unpredictable and difficult undertaking in itself. This would require years of inventive

effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art is extremely unpredictable with regard to protein function in the absence of reliable information regarding the protein activity. Even very similar proteins, as shown by homology, may have very different functions (see Rost et al (J. Mol. Biol. (2002) 318(2):595-608). In the current case, where no specific information is known regarding the function of the protein in actual biological organisms, it is entirely unpredictable what function and activity will be found for this protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the protein.

This data further lacks any of the hallmarks of utility or of any enabled use because the overexpression of the nucleic acid is not relevant to the utility of the protein. There is no evidence that the protein itself is overexpressed. Meric et al (Molecular Cancer Therapeutics (2002) 1:971-979) in a discussion of regulation of gene activity in cancer notes that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation and protein stability (page 971, column 1)." So Meric teaches that there is not necessarily a correlation between mRNA levels and protein levels in cancer cells, since the regulation may occur at levels other than that of the mRNA, such as in the level of translation of the mRNA or in the stability of the protein.

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So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by Applicant showing overexpression of one component does not provide utility for the antibody to the protein itself.

So it is entirely unpredictable how one would use this antibody in any context whatsoever.

Working Examples

The specification has no working examples that relate to the antibody or protein. The nucleic acid working examples, showing overexpression in certain cancer cell lines, are not relevant for the reasons given above. Specifically, there is no statistical showing that the overexpression of the nucleic acids is even significant in any way. Even if the nucleic acid data is deemed significant, there is no showing that the results from nucleic acids have any correlation with the protein or antibody and the art cited above demonstrates that there is no presumption of such a correlation.

Guidance in the Specification.

The specification provides no specific or substantial uses for the PRO-539 antibody or protein.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Declaration

4. The Declarations under 37 CFR 1.132 filed July 15, 2004 are insufficient to overcome the rejection of the claims based upon 35 U.S.C. 101 as set forth in the last Office action for the following reasons.

The Declarations are fundamentally flawed because they fail to provide specific evidence regarding Pro-539. Each Declaration, the Polakis Declaration, the Goddard Declaration, the Grimaldi Declaration and the Ashkenazi Declaration state that, generically, increased mRNA levels may predict increased protein levels. However, besides the three references cited in the rejection, the declarations themselves support the position that the increase is not necessarily correlative. In the Polakis declaration, the Declarant notes at page 2 that about 80% of the mRNAs had expression levels which correlate with the expression level of the proteins, meaning that in this sample, 20% did of the mRNAs had expression levels which did NOT correlate with the protein expression levels.

So each Declaration represents solely the opinion of the Declarant regarding proteins in general, not Pro-539 in particular. There is no specific declaration which states that Pro-539 is overexpressed. There is no evidence of record that Pro-539 is overexpressed. There is significant evidence cited in the rejection, and found in the Declarations, that it is not inherent that mRNA overexpression yields protein overexpression. This is the factual conclusion which may be drawn from these declarations.

Response to Arguments

5. Applicant's arguments filed July 15, 2004 have been fully considered but they are not persuasive.

Applicant then argues the legal conclusion of lack of utility based upon the factual predicate discussed above in the response to declarations that while there can be a relationship between mRNA and protein expression, it is not inherent that mRNA overexpression yields protein overexpression

So when Applicant makes the statement that "The general, accepted understanding in the art is that the level of protein expression would therefore also be increased," this statement represents mere supposition. There is no evidence to support this specific assertion with regard to Pro-539. The Polakis declaration itself demonstrates that at least 20% of the time, using the samples of Applicant, this would not be true.

Further, there is no necessary expectation that the tumors or samples of Applicant are representative. As the cited prior art of Meric and Gokman-Polar make clear, it is not a predictable element whether increased mRNA levels yield increased protein expression levels.

In analyzing utility, the first place to begin is with the decision of the Supreme Court in Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). In Brenner, the Court concluded that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to

this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.”

Id. at 534-35, 148 USPQ at 695.

There is no specific benefit, in currently available form, for the Pro-539 protein or antibody, since there are no specific and substantial utilities for that Pro-539 protein or antibody.

The CCPA first applied Brenner in In re Kirk, 376 F.2d 936, 153 USPQ 48 (CCPA 1967). The invention claimed in Kirk was a set of steroid derivatives said to have valuable biological properties and to be of value “in the furtherance of steroidal research and in the application of steroidal materials to veterinary or medical practice.” Id. at 938, 153 USPQ at 50. The claims had been rejected for lack of utility. In response, the applicants submitted an affidavit which purportedly “show[ed] that one skilled in the art would be able to determine the biological uses of the claimed compounds by routine tests.” Id. at 939, 153 USPQ at 51.

The court held that “nebulous expressions [like] ‘biological activity’ or ‘biological properties’” did not adequately convey how to use the claimed compounds. Id. at 941, 153 USPQ at 52. Nor did the applicants’ affidavit help their case: “the sum and substance of the affidavit appear[ed] to be that one of ordinary skill in the art would know ‘how to use’ the compounds to find out in the first instance whether the compounds are—or are not—in fact useful or possess useful properties, and to ascertain what those properties are.” Id. at 942, 153 USPQ at 53.

The Kirk court held that an earlier CCPA decision, holding that a chemical compound meets the requirements of § 101 if it is useful to chemists doing research on steroids, had effectively been overruled by Brenner. "There can be no doubt that the insubstantial, superficial nature of vague, general disclosures or arguments of 'useful in research' or 'useful as building blocks of value to the researcher' was recognized, and clearly rejected, by the Supreme Court" in Brenner. See Kirk, 376 F.2d at 945, 153 USPQ at 55.

The current situation is identical to that in Kirk. The Declarations filed provide evidence that one could determine whether the Pro-539 protein is useful, but do not even show any utility specifically for Pro-539 as discussed above. Further, the discussion cited by Applicant of the various declarations, such as the discussion on page 16 of the response, clearly represent language which is "useful in research" but has no current practical use. The speculation by the Declarants that medical practitioners might wish to know if proteins in general are overexpressed, without reference to Pro-539 in particular, is precisely the sort of vague argument which lacks any specificity.

There is no particular therapy associated with overexpression of the Pro-539 protein or antibody. There is no particular diagnosis associated with overexpression of the Pro-539 protein. There is no particular use whatsoever associated with overexpression of the Pro-539 protein or antibody. There are only vague general statements that such an overexpression might be useful in research or therapy. This is insufficient according to the Kirk court.

This is particularly demonstrated when Applicant argues that the proteins might be useful for tissue typing (see page 17). This is a classic throwaway utility since there is no evidence that Pro-539 protein is associated with any particular tissue at all.

Similarly, with regard to specific utility, the declaration, the arguments and the specification are entirely silent on any real specific utility for Pro-539. When Applicant states that "evidence of overexpression of PRO539 nucleic acids" provides utility to the protein or antibody, this presumes the protein is similarly overexpressed. As discussed at length above, this is not necessarily the case. Consequently, this cannot serve as a foundation stone to support specific utility.

Since Applicant's underlying arguments are not found persuasive for the reasons given above, the conclusion necessarily differs. For the reasons given above, the current claims lack specific and substantial utility.

With regard to enablement, fundamentally the same arguments apply, and this rejection is maintained for the same reasons as given above in response to the arguments on utility.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Jeffrey Fredman
Primary Examiner
Art Unit 1637
